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The long-term use of inhaled tobramycin in patients with cystic fibrosis

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Abstract

Tobramycin nebuliser solution (TNS) has been investigated in several clinical trials, including a large, placebo-controlled study that demonstrated efficacy over a 24-week period. The open-label extension phase of this trial enabled observations to be conducted for an additional period of almost 18 months. Patients from both treatment arms ($n=396$) entered the open-label phase and received up to nine 28-day on, 28-day off cycles of TNS 300 mg by aerosol twice daily (b.i.d.). Mean lung function in patients who had received placebo during the double-blind phase improved during the first three cycles of the open-label treatment. However, lung function in these patients did not recover to the levels seen in those patients who had received TNS throughout the double-blind and open-label phases. In both groups of patients, improvement was maintained during the study. Greater improvements were seen in adolescents compared with older patients. Adverse events were generally uncommon, with a notably lower incidence of fever, anorexia, abdominal pain and vomiting than was observed in the double-blind phase among patients who received placebo, and a generally low incidence of tinnitus. We conclude that long-term TNS administration is safe and effective.

Keywords: TOBI; Tobramycin; Cystic fibrosis; *Pseudomonas aeruginosa*; Aerosol antibiotics

1. Introduction

Patients with cystic fibrosis (CF) have long been recognized to succumb primarily to the gradual failure of their lungs related to chronic and recurrent airway infection, as well as gradual lung destruction. Patient survival has improved over the past 30 years [1], and this is partly due to the development of new antibiotics. However, infection with the most common airway pathogen, *Pseudomonas aeruginosa*, has been difficult to treat on an outpatient basis, since most of the effective drugs require intravenous administration. The administration of antibiotics by inhalation is potentially more effective and more convenient than intravenous administration [2]. Previously, tobramycin nebuliser solution (TNS) has been prepared by reconstituting intravenous tobramycin—a practice which is less than satisfactory due to the inefficiency of delivery and the potential for mucosal irritation. However, over the last 8 years a new formulation of tobramycin has been specifically developed for administration by aerosol (TOBI®) (see Smith, elsewhere in this supplement). This was tested in a 24-week, double-blind, randomized, placebo-controlled, multi-center study [3] which found that TNS was well-tolerated and was associated with improved pulmonary function, decreased *P. aeruginosa* density in the sputum, and decreased risk of hospitalization.

In addition to the 24-week, double-blind phase, the protocol for this study allowed for an open-label extension for a period of almost 18 months. The extension phase allowed further data to be collected on the long-term use of TNS (in both patient groups from the original study), as well as providing an opportunity to study the effect of TNS administration in adolescent patients. This paper presents the results of this extension phase.

2. Methods

The initial, double-blind, randomized study recruited 520 patients at 69 centers over the course of approximately 1 year [3]. In order to be included in the study, the patients had to have a documented diagnosis of CF, moderate to severe lung impairment with FEV_1 values of 25–75% predicted, and documented *P. aeruginosa* infection. They needed to be at least 6 years of age and relatively stable. Exclusion criteria included significant haemoptysis, significant hypoxemia, hypersensitivity to

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Table 1
Patient characteristics at baseline[a]

Characteristic	TNS ($n=258$)	Conventional care/placebo ($n=262$)
Male, *n* (%)	149 (58%)	132 (50%)
Age mean ± S.D. (years)	20.8 ± 9.5	20.6 ± 10.0
6–12 years, *n* (%)	55 (21%)	61 (23%)
13–17 years, *n* (%)	63 (24%)	67 (26%)
≥18 years, *n* (%)	140 (54%)	134 (51%)
Use of dornase alfa, *n* (%)	198 (77%)	204 (78%)
FEV_1[b] (no. tested)	257	262
Mean ± S.D.—% of predicted	49.9 ± 15.5	51.2 ± 16.8

[a] Adapted from table 1 in Döring et al. [2].
[b] FEV_1 = forced expiratory volume in 1 s.

aminoglycosides, recent pulmonary deterioration, impaired renal function, or the presence of *Burkholderia cepacia* in the airway in the last 2 years. Susceptibility of *P. aeruginosa* organisms to tobramycin was not a criterion. Informed consent was obtained from the patients, parents or guardians, as appropriate for age.

On entry, patients were randomized into two groups—conventional therapy, plus a placebo aerosol of quinine (1.25 mg quinine sulfate in 5 ml, one-quarter normal saline) by inhalation twice daily (the 'placebo group'), and conventional therapy plus TNS 300 mg in 5 ml b.i.d. by aerosol (the 'TNS group').

Patients who completed the double-blind, 24-week study were offered the opportunity to enter another 48-week study in which they would receive open-label TNS 300 mg b.i.d. by aerosol. Patients who completed the 48-week open-label study were then offered the opportunity to participate in a second open-label study lasting an additional 24 weeks.

The PARI LC PLUS jet nebulizer was used with a PulmoAide compressor for both groups throughout the entire study. The treatment aerosols were given twice daily for 4 weeks and then a 'drug vacation' was given for the following 4 weeks. Thus, patients who completed the entire study received 12 8-week cycles, comprising 4 weeks of inhaled drug followed by 4 weeks off. They either received TNS for all 12 cycles, or three cycles of placebo followed by nine of TNS.

Patients received the best available care from their physicians. They could be hospitalized and treated with any antibiotic necessary, including intravenous (IV) but excluding inhaled anti-pseudomonal antibiotics. Patients who were receiving dornase alfa at entry to the study could continue to receive it during the study, although initiation of dornase alfa treatment during the study was not allowed.

Spirometry was performed at each clinic visit. Patients were monitored closely for improvements as well as the appearance of adverse events. Pulmonary function, clinical status, compliance with treatment, intercurrent illnesses, medication use and occurrence of adverse events were continually monitored throughout all three studies.

3. Results

Results are shown for the entire 2-year study period, including the initial 24-week double-blind phase and both subsequent open-label extension phases.

Table 1 indicates the demographics of the patients recruited. Their mean FEV_1 was approximately 50% predicted, suggesting that they would be likely to experience intermittent pulmonary deterioration and need hospitalization. Approximately 70% of both patient groups were receiving dornase alfa during the study.

Two hundred and fifty-eight patients were randomized to receive TNS and 262 patients received a placebo. The first open-label study began with 192 patients who had previously received TNS and 204 patients who had previously received a placebo. At the mid-point of the first open-label study (after three cycles), 157 of the original TNS patients and 155 of the initial placebo therapy patients remained. The final three-cycle study recruited 127 patients of the initial TNS recipients and 131 of the initial placebo patients.

Patients who received TNS showed improved FEV_1 in the first 2 weeks (Fig. 1). Although there was some variation in the degree of improvement, that improvement persisted through the third cycle of the drug. At the end of three cycles, the patients on TNS had a mean change in FEV_1 percentage predicted of 10.1%, compared with a change of −1.8% in the patients in the placebo group.

At the start of the open-label study period, the patients who had been receiving TNS continued to show mean FEV_1 values that, on average, remained above their baseline values. The patients who were crossed over from placebo to open-label TNS had a marked improvement in their pulmonary function. However, mean FEV_1 in the placebo group did not reach the levels seen in patients who had received with TNS in the initial,

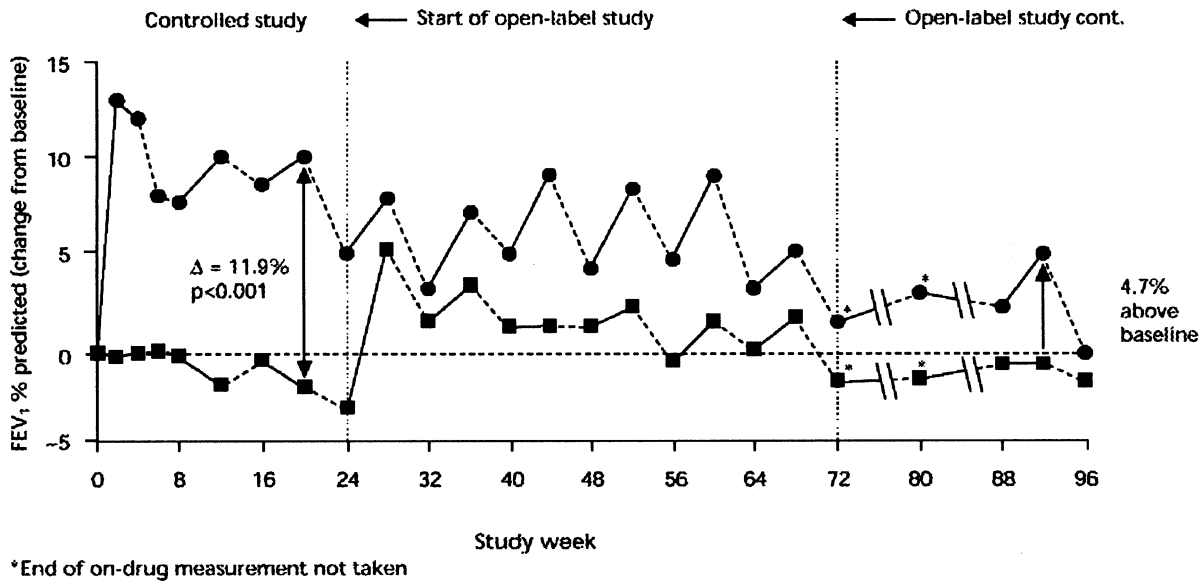

Fig. 1. Mean change in FEV_1% predicted during the course of the study in patients who received either TNS at all times (●) or placebo during the initial 24-week, double-blind phase and TNS for the remainder of the study (■). Solid lines represent periods on aerosol drug while dotted lines represent periods off aerosols. △ = Treatment effect (the change from baseline in the TNS less the change from baseline in the placebo group).

double-blind phase. By the end of the 12th treatment cycle, the mean FEV_1 in the TNS-only group was 4.7% above the baseline value at the start of the study. Mean FEV_1 at endpoint in patients in the placebo-TNS crossover group was slightly less than the baseline level, but was still greater than it had been at the end of the placebo phase (week 24).

In addition to improvement in the FEV_1, patients who were treated with TNS had a significant reduction in the number of courses of IV anti-pseudomonal antibiotic use per year. The 262 patients receiving conventional therapy and placebo aerosols required 1.9 courses of anti-pseudomonal antibiotics per patient per year, while the 518 patients receiving TNS (both the randomized and the open-label portions of the trial, regardless of initial study group assignment) required approximately 1.25 courses per patient per year.

Because of the fragile pulmonary status that is typical of teenagers, it was important to evaluate the effectiveness of TNS in adolescents. For this reason, a subgroup analysis was performed evaluating the change in FEV_1 for patients aged 13–17 years. As shown in Fig. 2, the adolescent patients treated with TNS from the beginning had a marked improvement of approximately 15% in their FEV_1 over the first three cycles of treatment. This contrasts with an approximately 8% decline in FEV_1 for the adolescent patients treated with placebo.

The patients who continued TNS maintained their level of improvement over the next nine cycles, ending with an FEV_1 that was still an average of 14.3% above their week 0 baseline after 12 cycles of TNS (almost 2 years). The group of adolescent patients who crossed over from the conventional therapy with placebo aerosol to receive TNS in the open-label phase showed a marked improvement during subsequent cycles. This degree of improvement was similar to that seen in the group who started on TNS in the double-blind study. Of importance, the mean FEV_1 values of this crossover group after nine cycles (72 weeks) of TNS were maintained at levels above those at the start of the open-label part of the study.

During the course of the study, numerous evaluations for adverse events were performed. Fig. 3 shows the six types of adverse events that occurred with significant difference in frequency between the patients receiving TNS (at any time, regardless of initial treatment group assignment) and the patients receiving conventional therapy with placebo aerosols during the first three drug cycles.

Fever, anorexia, abdominal pain and vomiting all occurred more commonly in patients receiving conventional therapy with placebo aerosols than in those who were receiving TNS. Voice alteration and tinnitus occurred more frequently in patients who were receiving TNS compared with those in the conventional therapy/placebo aerosol portion of the study. The incidence of voice alteration decreased as the duration of TNS use increased. Ultimately, after using TNS for nearly 2 years, the incidence of voice alteration was lower than it was for the initial three cycles of patients receiving conventional therapies with placebo aerosols. The incidence of hearing loss in patients receiving conventional therapy

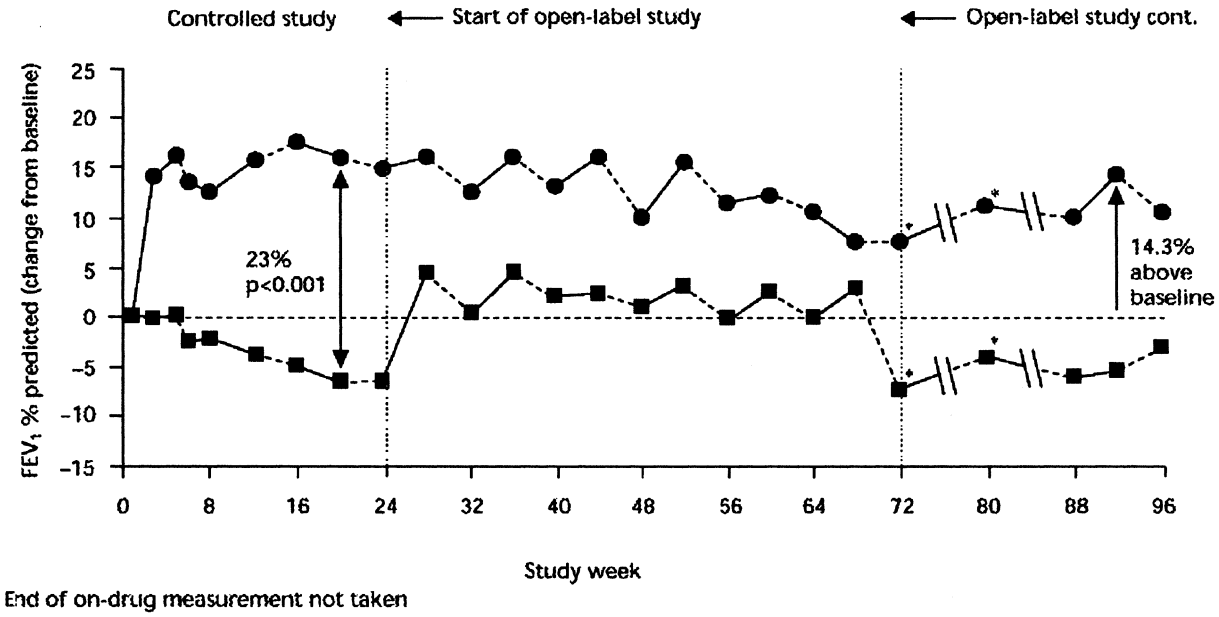

Fig. 2. Mean change in FEV_1% predicted in adolescent patients (aged 13–17 years) who received either TNS at all times (●) or placebo during the initial 24-week, double-blind phase and TNS for the remainder of the study (■). Solid lines represent periods on aerosol drug while dotted lines represent periods off aerosols).

with placebo aerosols was 1.1%, and it ranged from <1% to a maximum of 1.4% in the various cycles of patients receiving TNS. No events of hearing loss appeared to be related to TNS use; they were instead related to otitis media and/or the use of IV aminoglycosides. Audiograms showing ≥15 dB bilateral decrease in hearing were observed in only two patients. Both were judged by the investigators at the site to be transient effects not attributed to TNS. Both patients completed the 96-week study.

4. Discussion

This study shows that it is possible to maintain for at least 2 years the benefits previously demonstrated by Ramsey et al. [3] in the use of TNS for three 8-week drug cycles (4 weeks on, 4 weeks off).

The patients treated in this study were typical of patients in most CF clinics, with a mean age of approximately 20 years and a mean FEV_1 of approximately 50% predicted. Patients initially treated with TNS con-

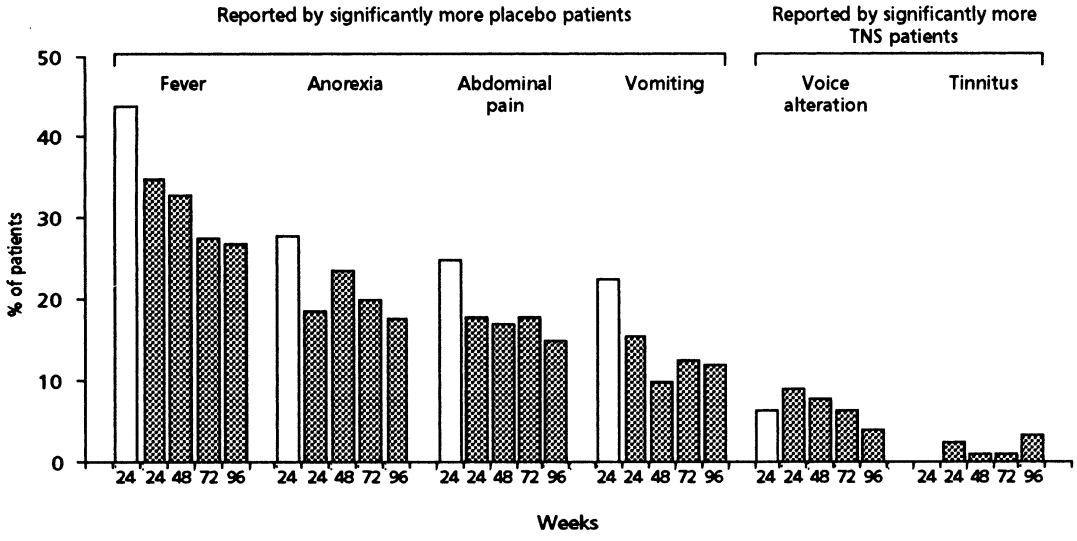

Fig. 3. The incidence of adverse events in patients receiving TNS at any time (■) compared with the incidence of adverse events reported during the double-blind phase by patients receiving placebo (□). Only those adverse events that occurred with significantly different ($P<0.05$) frequencies between the two groups are shown.

tinued to have improved pulmonary function 92 weeks after the start of the study compared to their values at week 0. When patients crossed over to TNS after the initial 24 weeks on conventional therapy with placebo aerosols, they showed an improvement that was similar to that of the patients who started on TNS on day 0. It is thus clear that patients with moderately-severe CF lung disease experience improved lung function as a result of the inhalation of TNS on an alternate month format.

The benefits that accrued to the subgroup of adolescent patients receiving TNS were nearly twice the benefits shown in the TNS group as a whole. This is particularly striking in comparison with the conventional therapy plus placebo group, in which the adolescent subgroup showed a more rapid rate of decline than that of the group as a whole. The group of teenage patients receiving TNS had improved pulmonary function (an average of 14.3% above baseline) 92 weeks after starting the treatment.

Patients in the TNS group had a lesser requirement for intravenous antibiotics to treat pseudomonal infections. Patients receiving TNS, whether in the randomized portion or the open-label portion of the study, needed only approximately two-thirds the number of IV antibiotic courses to treat *P. aeruginosa* infection compared with patients who received conventional therapy and placebo.

The safety data reported suggest that TNS was generally well-tolerated by the patients who received it. The fact that four types of adverse events (fever, anorexia, abdominal pain and vomiting) were more common in patients receiving conventional therapy and placebo aerosols than in patients receiving TNS suggests that TNS may actually improve overall patient comfort and metabolism. The problems of voice alteration and tinnitus, which occurred more commonly in patients on TNS, were relatively mild and transient.

In conclusion, this three-phase study of patients treated with TNS aerosols every other month for as long as 96 weeks showed that TNS is an effective and safe mode of therapy for patients with CF. The improvement shown in patients who took TNS after initially receiving conventional therapy with placebo aerosols demonstrates that the benefits of TNS, shown by Ramsey et al. [3], could be maintained for nearly 2 years, and that these benefits were not limited to the group of 258 patients initially treated with TNS. Furthermore, the open-label studies clearly demonstrate the remarkable benefit TNS holds for adolescent patients. These studies also provide stronger evidence that TNS causes few side-effects and may actually lessen the incidence of various systemic complaints. Further studies are needed to document the long-term effects of TNS on the typical gradual deterioration in lung function, on improvement in patient quality of life and on patient safety.

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